

SUPPLEMENTARY INFORMATION

doi:10.1038/nature18283

Supplementary Table 1 – Pathway analysis of genes altered by WNV-NS5-E218A compared to mock-infected controls at 25 days post-infection. KEGG pathway analysis using DAVID bioinformatics database functional annotation tool v.6.7. Analysis generated with list of genes having greater than 1.5 fold change and false discovery rate q value of less than 0.05 in Mock vs. WNV-all analysis. Adjusted p-values determined by Benjamini false discovery rate.

Pathway	genes	p- val	Adj p- val	Select Genes within pathway
Systemic lupus erythematosus	23	1.9E-14	0.000	HIST1H4M, HIST1H2AD, GRIN2B, HIST1H4A, C2, HIST1H4I, C4A, C4B, FCGR4, H2-AB1, TRIM21, FCGR3, C1QA, IGHG, CD86, FCGR2B, H2-DMA
Antigen processing and presentation	20	2.0E-12	0.000	H2-K1, CD8B1, H2-M3, H2-D1, IFI30, H2-AB1, CTSS, H2-Q6, H2-Q7, CD74, B2M, TAPBP, H2-OA, PSME1, TAP2, TAP1, H2-EB1, H2-AA, H2-T23,
Allograft rejection	14	2.9E-09	0.000	H2-K1, H2-M3, H2-D1, H2-AB1, H2-Q6, H2-Q7, H2-Q8, IGHG, CD86, H2-OA, H2-EB1, H2-AA, H2-T23, H2-T10, H2-DMA, IGH-VJ558
Cytokine-cytokine receptor interaction	26	6.2E-09	0.000	CCL2, IL21R, CXCL9, CXCR3, CCL5, TNFRSF4, CCL7, CXCL10, IL10RA, TNFRSF18, CSF3R, IL2RG, IFNGR1, CD27, CSF1R, TGFB2, CCL19
Natural killer cell mediated cytotoxicity	18	2.2E-08	0.000	H2-K1, PIK3CG, PTPN6, CD244, H2-D1, FCGR4, VAV1, HCST, FCGR3, IGHG, RAC2, LCK, PLCG2, FCER1G, H2-T23, IFNGR1, IGH-VJ558, SH3BP2
Viral myocarditis	16	2.4E-08	0.000	H2-K1, H2-M3, H2-D1, H2-AB1, H2-Q6, H2-Q7, H2-Q8, IGHG, CD86, RAC2, H2-OA, CASP8, H2-EB1, H2-AA, H2-T23, H2-T10, H2-DMA
Autoimmune thyroid disease	14	4.8E-08	0.000	H2-K1, H2-M3, H2-D1, H2-AB1, H2-Q6, H2-Q7, H2-Q8, IGHG, CD86, H2-OA, H2-EB1, H2-AA, H2-T23, H2-T10, H2-DMA, IGH-VJ558
Chemokine signaling pathway	21	7.4E-08	0.000	PIK3CG, CCL2, ADCY7, CXCL9, CXCR3, STAT1, CCL5, CCL4, VAV1, PRKCD, WAS, CCL7, STAT2, CXCL10, RAC2, CCR5, CXCL13, CXCL16, CX3CR1
Graft-versus-host disease	12	3.2E-07	0.000	H2-K1, H2-M3, H2-D1, H2-AB1, H2-Q6, H2-Q7, H2-Q8, CD86, H2-OA, H2-EB1, H2-AA, H2-T23, H2-T10, H2-DMA
Primary immunodeficiency	10	3.2E-07	0.000	IGHG, CD8B1, CD3D, CD3E, TAP2, TAP1, TNFRSF13B, LCK, IL2RG, IGH-VJ558
Cell adhesion molecules (CAMs)	18	7.1E-07	0.000	H2-K1, CD8B1, H2-M3, H2-D1, H2-AB1, H2-Q6, H2-Q8, VCAM1, CD86, H2-OA, CD274, H2-EB1, CD2, H2-T10, CD6, H2-DMA, SELPLG
Type I diabetes mellitus	12	7.7E-07	0.000	H2-K1, H2-M3, H2-D1, H2-AB1, H2-Q6, H2-Q7, H2-Q8, CD86, H2-OA, H2-EB1, H2-AA, H2-T23, H2-T10, H2-DMA
B cell receptor signaling pathway	13	1.3E-06	0.000	PIK3CG, PTPN6, IFITM1, CD72, VAV1, IGHG, FCGR2B, RAC2, PLCG2, PIK3AP1, CD79B, INPP5D, IGH-VJ558
Intestinal immune network for IgA production	10	1.2E-05	0.000	IGHG, CD86, TNFSF13B, H2-OA, LOC641240, TNFRSF13B, H2-EB1, H2-AA, H2-AB1, H2-DMA, IGH-VJ558
Toll-like receptor signaling pathway	13	1.3E-05	0.000	PIK3CG, TLR2, CXCL9, CCL5, TLR6, STAT1, CCL4, CXCL10, CD86, MYD88, IRF5, IRF7, CASP8
Hematopoietic cell lineage	12	1.4E-05	0.000	CD3G, CD8B1, CD3D, CD3E, CD9, IGHG, H2-EB1, CD2, CSF3R, H2-AA, IGH-VJ558, CSF1R
Asthma	8	2.3E-05	0.000	IGHG, H2-OA, H2-EB1, H2-AA, FCER1G, H2-AB1, H2-DMA, IGH-VJ558
Cytosolic DNA-sensing pathway	8	6.5E-04	0.004	DDX58, IRF7, TREX1, CCL5, CASP1, CCL4, CXCL10, ADAR
Fc gamma R-mediated phagocytosis	10	1.3E-03	0.007	PIK3CG, IGHG, RAC2, FCGR2B, PLCG2, INPP5D, WAS, PRKCD, VAV1, IGH-VJ558
Fc epsilon RI signaling pathway	9	1.6E-03	0.009	PIK3CG, IGHG, RAC2, PLCG2, FCER1G, INPP5D, PRKCD, VAV1, IGH-VJ558
Complement and coagulation cascades	8	4.0E-03	0.021	C1QA, VWF, C1QB, C4A, C4B, SERPING1, C2, PROS1, C1QC
Jak-STAT signaling pathway	11	8.1E-03	0.040	IRF9, PIK3CG, PTPN6, IL10RA, IL21R, CSF3R, IL2RG, STAT1, CISH, IFNGR1, STAT2

Supplementary Table 2 – Transcriptionally altered genes by microarray, WNV-poor higher than WNV-Good. Genes higher in WNV-poor than in WNV-good (top 100 genes by fold change and p value <0.05)

Rank	Gene	Definition	Fold ch	p
1	LOC636875	PREDICTED: similar to Ig kappa chain V-V region L7 precursor (LOC636875)	8.68	0.037
2	LOC100046552	PREDICTED: similar to Unknown (protein for MGC:103328) (LOC100046552)	7.81	0.043
3	IGHG	PREDICTED: Immunoglobulin heavy chain (gamma polypeptide) (Ighg)	6.91	0.004
4	IGH-VJ558		5.99	0.013
5	LOC381774		5.79	0.036
6	IGK-V5	PREDICTED: immunoglobulin kappa chain variable 5 (V5 family) (Igk-V5)	5.51	0.042
7	IGK-V5	PREDICTED: immunoglobulin kappa chain variable 5 (V5 family) (Igk-V5)	5.46	0.010
8	LOC207685	PREDICTED: hypothetical protein LOC207685, transcript variant 1 (LOC207685)	4.75	0.018
9	IGH-VJ558	PREDICTED: immunoglobulin heavy chain (J558 family) (Igh-VJ558)	4.71	0.016
10	LOC100047316	PREDICTED: similar to anti-MOG Z12 variable light chain (LOC100047316)	4.15	0.007
11	AI324046		4.00	0.035
12	AI324046		3.98	0.041
13	LOC386520		3.80	0.006
14	IGHV1S119_L33961_IG_HEAVY_VARIABLE_1S119_14		3.78	0.020
15	AI324046		3.57	0.019
16	LOC380801		3.53	0.011
17	LOC385109		3.47	0.018
18	SAA3	serum amyloid A 3 (Saa3)	3.46	0.046
19	LOC100047162	PREDICTED: similar to immunoglobulin kappa-chain (LOC100047162)	3.33	0.033
20	LOC640696	PREDICTED: similar to Ig heavy chain V-I region V35 precursor (LOC640696)	3.29	0.032
21	LOC636752	PREDICTED: similar to Ig kappa chain V-VI region NQ2-6.1 (LOC636752)	3.28	0.002
22	AI324046		3.26	0.042
23	IGLC2_J00595_IG_LAMBDA_CONSTANT_2_14		3.14	0.006
24	LOC669053	PREDICTED: similar to Ig kappa chain V-V region MPC11 precursor (LOC669053)	3.04	0.034
25	LOC630302	PREDICTED: similar to VH283 protein (LOC630302)	3.00	0.037
26	IGHG	PREDICTED: Immunoglobulin heavy chain (gamma polypeptide), transcript variant 1 (Ighg)	2.97	0.030
27	LOC100048770	PREDICTED: similar to Ig H-chain V-JH1-region (LOC100048770)	2.96	0.020
28	IGHV1S133_AF304553_IG_HEAVY_VARIABLE_1S133_89		2.93	0.001
29	GBP2	guanylate binding protein 2 (Gbp2)	2.84	0.037
30	SLPI	secretory leukocyte peptidase inhibitor (Slpi)	2.77	0.035
31	LOC385277		2.71	0.026
32	SERPING1	serine peptidase inhibitor 1 (C1 inhibitor)	2.68	0.043
33	UBD	ubiquitin D (Ubd)	2.52	0.046
34	IGHV1S59_L17134_IG_HEAVY_VARIABLE_1S59_150		2.46	0.008
35	LOC383196	PREDICTED: hypothetical LOC383196 (LOC383196)	2.44	0.002
36	IGKV4-71_AJ231218_IG_KAPPA_VARIABLE_4-71_20		2.38	0.017
37	1110059M19RIK		2.37	0.040
38	LOC383196	PREDICTED: hypothetical LOC383196 (LOC383196)	2.37	0.001
39	LOC100042270	PREDICTED: similar to Unknown (protein for MGC:41421) (LOC100042270)	2.30	0.001
40	DISP2	dispatched homolog 2 (Drosophila) (Disp2)	2.27	0.008
41	TSPO	translocator protein (Tspo)	2.26	0.026
42	IFITM1	interferon induced transmembrane protein 1 (Ifitm1)	2.25	0.013
43	PSMB8		2.25	0.036
44	CD274	CD274 antigen (Cd274)	2.20	0.039
45	TUBA6		2.17	0.041
46	IGHV1S30_X02462_IG_HEAVY_VARIABLE_1S30_12		2.16	0.046
47	IGKV4-91_AJ231229_IG_KAPPA_VARIABLE_4-91_29		2.13	0.033
48	CXCL10	chemokine (C-X-C motif) ligand 10 (Cxcl10)	2.12	0.045
49	PIK3AP1	phosphoinositide-3-kinase adaptor protein 1 (Pik3ap1)	2.10	0.044
50	H2-T10	histocompatibility 2, T region locus 10 (H2-T10)	2.10	0.039
51	IGHV1S34_X02467_IG_HEAVY_VARIABLE_1S34_71		2.10	0.050
52	MVP	major vault protein (Mvp)	2.09	0.039
53	CYTIP	cytogenetic translocation breakpoint interacting protein (Cytip)	2.09	0.025
54	PRG4		2.06	0.033
55	LOC434609	PREDICTED: similar to Ig heavy chain V region VH558 A1/A4 precursor (LOC434609)	2.05	0.001
56	CD52		2.04	0.030
57	EGR2		2.03	0.025

58	IGHA_J00475\$V00785_IG_HEAVY_CONSTANT_ALPHA_135		2.02	0.001
59	TSPO	translocator protein (Tspo)	1.99	0.030
60	SULF1	sulfatase 1 (Sulf1)	1.96	0.037
61	4930533K18RIK		1.93	0.006
62	2810046M22RIK		1.91	0.041
63	LY6C1	lymphocyte antigen 6 complex, locus C1 (Ly6c1)	1.89	0.037
64	CDKN1A	cyclin-dependent kinase inhibitor 1A (P21) (Cdkn1a)	1.89	0.046
65	HDC	histidine decarboxylase (Hdc)	1.88	0.013
66	GIMAP6	GTPase, IMAP family member 6 (Gimap6)	1.86	0.013
67	VAMP8	vesicle-associated membrane protein 8 (Vamp8)	1.85	0.022
68	TCEA3		1.83	0.015
69	LCK	lymphocyte protein tyrosine kinase (Lck)	1.83	0.031
70	MIA1		1.82	0.044
71	GM1276	PREDICTED: gene model 1276, (NCBI) (Gm1276)	1.82	0.047
72	IFITM1	interferon induced transmembrane protein 1 (Ifitm1)	1.81	0.038
73	TRAF1		1.81	0.021
74	IGHV1S12_J00507_IG_HEAVY_VARIABLE_IS12_239		1.81	0.001
75	H2-DMA	histocompatibility 2, class II, locus DMA (H2-DMA)	1.81	0.047
76	LOC100048556	PREDICTED: similar to monocyte chemoattractant protein-5, (LOC100048556)	1.80	0.039
77	SYNPO		1.80	0.030
78	TNF	tumor necrosis factor (Tnf)	1.78	0.037
79	LOC100048556	PREDICTED: similar to monocyte chemoattractant protein-5, (LOC100048556)	1.78	0.023
80	TAPBP		1.78	0.005
81	LOC223672		1.77	0.041
82	SELL	selectin, lymphocyte (Sell)	1.75	0.043
83	1700024G13RIK		1.73	0.003
84	LBP	lipopolysaccharide binding protein (Lbp)	1.73	0.040
85	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (Nfkbia)	1.72	0.042
86	LOC100038882	PREDICTED: hypothetical protein LOC100038882 (LOC100038882)	1.72	0.031
87	IL1A	interleukin 1 alpha (Il1a)	1.72	0.015
88	ECM1	extracellular matrix protein 1 (Ecm1)	1.69	0.048
89	MIA1	melanoma inhibitory activity 1 (Mia1)	1.69	0.031
90	ONECUT3	one cut domain, family member 3 (Onecut3)	1.69	0.040
91	TRIOBP		1.68	0.045
92	CPT1A		1.68	0.014
93	INPP5D	inositol polyphosphate-5-phosphatase D (Inpp5d)	1.68	0.047
94	LOC100040402	PREDICTED: hypothetical protein LOC100040402 (LOC100040402)	1.67	0.039
95	TAP2	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP) (Tap2)	1.67	0.028
96	2600011C06RIK		1.65	0.044
97	TNFSF13B	tumor necrosis factor (ligand) superfamily, member 13b (Tnfsf13b)	1.65	0.044
98	B930097J01RIK		1.64	0.027
99	TNFRSF12A	tumor necrosis factor receptor superfamily, member 12a (Tnfrsf12a)	1.64	0.040
100	LASS2	LAG1 homolog, ceramide synthase 2 (Lass2)	1.64	0.004

Supplementary Table 3 – Transcriptionally altered genes by microarray, WNV-good higher than WNV-Poor. Genes higher in WNV-good than in WNV-poor (top 100 genes by fold change and p value <0.05)

Rank	Gene	Definition	Fold ch	p
1	LOC232065		2.49	0.019
2	CYFIP2	cytoplasmic FMR1 interacting protein 2 (Cyfip2)	1.97	0.000
3	PHF14	PHD finger protein 14 (Phf14)	1.95	0.009
4	5430417J04RIK		1.86	0.009
5	AU021092	expressed sequence AU021092 (AU021092)	1.82	0.002
6	PPAP2A	phosphatidic acid phosphatase 2a (Pppap2a), transcript variant 2	1.78	0.013
7	ROCK2	Rho-associated coiled-coil containing protein kinase 2 (Rock2)	1.78	0.002
8	TRMT2B	TRM2 tRNA methyltransferase 2 homolog B (S. cerevisiae) (Trmt2b)	1.74	0.006
9	CHRNA1	cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle) (Chrna1)	1.73	0.000
10	SQLE	squalene epoxidase (Sqle)	1.73	0.021
11	TTC30A1	tetratricopeptide repeat domain 30A1 (Ttc30a1)	1.72	0.004
12	SC4MOL	sterol-C4-methyl oxidase-like (Sc4mol)	1.69	0.046
13	2610044O15RIK	RIKEN cDNA 2610044O15 gene (2610044O15Rik)	1.68	0.013
14	GPR155	G protein-coupled receptor 155 (Gpr155) XM_921852 XM_921857	1.65	0.019
15	CCDC25	coiled-coil domain containing 25 (Ccdc25)	1.65	0.001
16	WDR17	WD repeat domain 17 (Wdr17)	1.65	0.042
17	PDGFRL	platelet-derived growth factor receptor-like (Pdgfrl)	1.65	0.023
18	RLBP1L1	retinaldehyde binding protein 1-like 1 (Rlpb1l1)	1.65	0.000
19	B230107J06RIK		1.63	0.003
20	LOC382964		1.63	0.020
21	STX3	syntaxin 3 (Stx3), transcript variant B	1.63	0.005
22	CYB561D2	cytochrome b-561 domain containing 2 (Cyb561d2)	1.63	0.012
23	PDIK1L	PDLIM1 interacting kinase 1 like (Pdk1l)	1.63	0.001
24	RASL12	RAS-like, family 12 (Rasl12)	1.63	0.004
25	LOC100046855	PREDICTED: similar to BKL (LOC100046855)	1.63	0.001
26	6430531H12RIK		1.63	0.003
27	TESC		1.62	0.018
28	4631422C13RIK	PREDICTED: RIKEN cDNA 4631422C13 gene (4631422C13Rik)	1.62	0.015
29	UBE3A	ubiquitin protein ligase E3A (Ube3a), transcript variant 2	1.61	0.030
30	GUCY2E		1.61	0.005
31	DOC2B	double C2, beta (Doc2b)	1.60	0.035
32	ARHGEF9	CDC42 guanine nucleotide exchange factor (GEF) 9 (Arhgef9)	1.60	0.016
33	CCNLJ	cyclin J-like (Ccnlj)	1.58	0.001
34	SEMA6C	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C (Sema6c)	1.58	0.029
35	TPPP	tubulin polymerization promoting protein (Tppp)	1.58	0.005
36	DOCK9	dicator of cytokinesis 9 (Dock9), transcript variant 1	1.58	0.012
37	4921521J11RIK		1.58	0.026
38	GRIN1	glutamate receptor, ionotropic, NMDA1 (zeta 1) (Grin1)	1.57	0.025
39	SIAH1B	seven in absentia 1B (Siah1b)	1.57	0.043
40	ALDH3A2		1.57	0.010
41	A430010E21RIK		1.56	0.007
42	DOC2B	double C2, beta (Doc2b)	1.56	0.014
43	TERF2IP	telomeric repeat binding factor 2, interacting protein (Terf2ip)	1.56	0.029
44	TCF20	transcription factor 20 (Tcf20)	1.56	0.022
45	KLRB1B	killer cell lectin-like receptor subfamily B member 1B (Krb1b)	1.56	0.020
46	VT1A		1.56	0.001
47	CHST7	carbohydrate (N-acetylglucosamino) sulfotransferase 7 (Chst7)	1.56	0.019
48	2010011I20RIK	RIKEN cDNA 2010011I20 gene (2010011I20Rik)	1.56	0.039
49	PCDHAC1	protocadherin alpha subfamily C, 1 (Pcdhac1)	1.55	0.025
50	4930503L19RIK	RIKEN cDNA 4930503L19 gene (4930503L19Rik) XM_001001515	1.55	0.046
51	HSPA12A	heat shock protein 12A (Hspa12a)	1.55	0.045
52	LOC100047052	PREDICTED: similar to Aptx protein (LOC100047052)	1.55	0.006
53	GALNT3		1.55	0.010
54	ALG8	asparagine-linked glycosylation 8 homolog (yeast, alpha-1,3-glucosyltransferase) (Alg8)	1.54	0.012
55	LOC235086		1.54	0.014
56	TTLL9	tubulin tyrosine ligase-like family, member 9 (Ttl9), transcript variant 1	1.54	0.043
57	PPP2R2C	protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), gamma isoform (Ppp2r2c)	1.54	0.018

58	ROBO1	roundabout homolog 1 (Drosophila) (Robo1)	1.53	0.048
59	ELFN2	leucine rich repeat and fibronectin type III, extracellular 2 (Elfn2)	1.53	0.020
60	EG406223	predicted gene, EG406223 (EG406223)	1.53	0.012
61	2210008F06RIK	PREDICTED: RIKEN cDNA 2210008F06 gene (2210008F06Rik)	1.53	0.039
62	PVRL3	poliovirus receptor-related 3 (Pvrl3), transcript variant alpha	1.53	0.044
63	RNF123	ring finger protein 123 (Rnf123)	1.53	0.000
64	5830435K17RIK		1.52	0.025
65	RTN4	reticulon 4 (Rtn4), transcript variant 1	1.52	0.016
66	SEMA3E	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3E (Sema3e)	1.52	0.018
67	PPP4R4	protein phosphatase 4, regulatory subunit 4 (Ppp4r4)	1.52	0.030
68	COVA1	cytosolic ovarian carcinoma antigen 1 (Cova1)	1.51	0.016
69	6030419L17RIK		1.51	0.003
70	POPDC3	popeye domain containing 3 (Popdc3)	1.51	0.049
71	XKR7	X Kell blood group precursor related family member 7 homolog (Xkr7)	1.51	0.031
72	CCDC94	coiled-coil domain containing 94 (Ccdc94)	1.51	0.024
73	E130309D02RIK	RIKEN cDNA E130309D02 gene (E130309D02Rik)	1.51	0.004
74	1700020L24RIK	RIKEN cDNA 1700020L24 gene (1700020L24Rik)	1.51	0.006
75	SGTB	small glutamine-rich tetratricopeptide repeat (TPR)-containing, beta (Sgtb)	1.50	0.003
76	CHD5	chromodomain helicase DNA binding protein 5 (Chd5), transcript variant 1	1.50	0.012
77	RIC3	resistance to inhibitors of cholinesterase 3 homolog (C. elegans) (Ric3), transcript variant 2	1.50	0.019
78	KCNIP2	Kv channel-interacting protein 2 (Kcnip2), transcript variant a	1.50	0.008
79	NCKAP1	NCK-associated protein 1 (Nckap1)	1.50	0.017
80	GRHL1	grainyhead-like 1 (Drosophila) (Grhl1)	1.50	0.044
81	D030013I16RIK	RIKEN cDNA D030013I16 gene (D030013I16Rik)	1.49	0.005
82	ARL3	ADP-ribosylation factor-like 3 (Arl3)	1.49	0.032
83	P115	peptidase inhibitor 15 (Pi15)	1.49	0.012
84	SNAP91	synaptosomal-associated protein 91 (Snap91)	1.49	0.017
85	SEZ6L2	seizure related 6 homolog like 2 (Sez6l2)	1.49	0.018
86	BC030500	cDNA sequence BC030500 (BC030500)	1.48	0.042
87	6030405A18		1.48	0.028
88	MCRS1	microspherule protein 1 (Mcrs1)	1.48	0.011
89	LAMA4	laminin, alpha 4 (Lama4)	1.48	0.026
90	GDA	guanine deaminase (Gda)	1.48	0.018
91	PARP1	poly (ADP-ribose) polymerase family, member 1 (Parp1)	1.48	0.004
92	MAPK8IP1	mitogen-activated protein kinase 8 interacting protein 1 (Mapk8ip1)	1.48	0.023
93	DLX2	distal-less homeobox 2 (Dlx2)	1.48	0.020
94	ISLR2	immunoglobulin superfamily containing leucine-rich repeat 2 (Islr2)	1.48	0.003
95	TGFB2	transforming growth factor, beta 2 (Tgfb2)	1.48	0.008
96	LOC100045726	PREDICTED: hypothetical protein LOC100045726 (LOC100045726)	1.48	0.009
97	9130213B05RIK	RIKEN cDNA 9130213B05 gene (9130213B05Rik)	1.48	0.041
98	NUFIP1	nuclear fragile X mental retardation protein interacting protein 1 (Nufip1)	1.47	0.022
99	CYB5D2	cytochrome b5 domain containing 2 (Cyb5d2)	1.47	0.005
100	ACO1	aconitase 1 (Aco1)	1.47	0.040

Supplementary Table 4. Pathway analysis of genes significantly altered in WNV-poor vs. WNV-good spatial memory performers at 25 days post-infection. KEGG pathway analysis using DAVID bioinformatics database functional annotation tool v.6.7. Analysis generated with list of genes having greater than 1.5 fold change and p value of less than 0.05 in WNV-poor vs. WNV-good analysis.

Adjusted p-values determined by Benjamini false discovery rate. Pathway lists were generated with the genes with greater expression in WNV-poor than WNV-good (top) and genes with greater expression in WNV-good than in WNV-poor learners (bottom).

WNV-Poor > WNV-Good

Rnk	Pathway	p val	Altered genes
1	Primary immunodeficiency	6.3E-04	LOC100048770, IGHG, LOC100048841, TAP2, LCK, AIRE, IGH-VJ558
2	Cytokine-cytokine receptor interaction	9.3E-04	IFNAB, TNF, CCL2, TNFRSF12A, IL21R, IL11RA1, TNFRSF4, CXCL10, CCL6, LEP, TNFRSF1A, TNFSF13B, FAS, IL1A
3	Natural killer cell mediated cytotoxicity	2.6E-03	IFNAB, LOC100048770, IGHG, CD244, TNF, ARAF, LCK, FAS, KLRA3, IGH-VJ558
4	Calcium signaling pathway	4.2E-03	LOC100048770, IGHG, EDNRB, GNA15, PDE1C, TACR1, CAMK2D, PLCD4, PLCD1, CHRNA7, CAMK2A, IGH-VJ558
5	Allograft rejection	5.4E-03	LOC100048770, IGHG, TNF, H2-T10, FAS, H2-DMA, IGH-VJ558
6	Graft-versus-host disease	5.4E-03	TNF, H2-T10, FAS, H2-DMA, IL1A, KLRA3
7	Apoptosis	7.1E-03	TNFRSF1A, IRAK3, TNF, NFKBIA, FAS, BIRC2, IL1A
8	Autoimmune thyroid disease	1.3E-02	IFNAB, LOC100048770, IGHG, H2-T10, FAS, H2-DMA, IGH-VJ558
9	B cell receptor signaling pathway	2.0E-02	LOC100048770, IGHG, IFITM1, NFKBIA, PIK3AP1, INPP5D, IGH-VJ558
10	Intestinal immune network for IgA production	2.1E-02	LOC100048770, IGHG, LOC100048841, TNFSF13B, H2-DMA, IGH-VJ558
11	Hematopoietic cell lineage	2.4E-02	LOC100048770, IGHG, TNF, ITGA1, IL11RA1, IL1A, IGH-VJ558
12	Asthma	2.6E-02	LOC100048770, IGHG, TNF, H2-DMA, IGH-VJ558
13	NOD-like receptor signaling pathway	3.3E-02	TNF, CCL2, ERBB2IP, NFKBIA, BIRC2
14	Type I diabetes mellitus	3.5E-02	TNF, H2-T10, FAS, H2-DMA, IL1A
15	Adipocytokine signaling pathway	4.2E-02	LEP, TNFRSF1A, TNF, NFKBIA, CPT1A

WNV-Good > WNV-Poor

Rnk	Pathway	p val	Altered genes
1	Long-term potentiation	0.002	GRM5, GRIN2B, GRIN1, PPP3CA, PPP1CC, PPP1CB, PRKCB
2	Calcium signaling pathway	0.013	TRPC1, PHKB, PDE1A, CACNA1G, RYR2, PRKCB, CACNA1B
3	Axon guidance	0.014	EPHA5, SEMA6C, PLXNA4, ROCK2, ROBO1, SEMA3E, SLIT2
4	Wnt signaling pathway	0.027	TBL1XR1, CCND1, ROCK2, SIAH1B, SIAH1A, CUL1, PRKCB
5	Terpenoid backbone biosynthesis	0.030	LOC100040592, MVD, FDPS
6	MAPK signaling pathway	0.035	MAPT, CACNA1G, PLA2G6, FGF13, MAPK8IP1, TGFB2
7	Butanoate metabolism	0.036	LOC100040592, GAD1, PDHB, ALDH3A2
8	Glyoxylate and dicarboxylate metabolism	0.039	GLYCTK, ACO1, AFMID
9	Steroid biosynthesis	0.043	TM7SF2, SQLE, SC4MOL
10	p53 signaling pathway	0.046	CCND1, SIAH1B, SIAH1A, CCNG2, ATM

Supplementary Table 5 – Human post-mortem tissue. Relevant information on human autopsy cases used in this study, including age, sex, post-mortem interval (PMI) in hours, cause of death, and other comorbidities noted. Abbreviations used: Pulseless electrical activity (PEA), Dentate Gyrus (DG), Entorhinal Cortex (Ent Ctx). Scoring = negative (-), mild (+), moderate (++) or severe (+++) for West Nile virus antigen immunostaining / and neuron loss.

<u>Group</u>	<u>Age</u>	<u>Sex</u>	<u>P.M.I</u>	<u>Cause of death</u>	<u>Other findings / Comorbidities</u>	<u>DG</u>	<u>CA2/3</u>	<u>CA1</u>	<u>Ent Ctx</u>
WNV	46	f	15	WNV encephalitis	History of non-Hodgkin's lymphoma, bone-marrow transplant recipient	- / -	+++ / ++	- / ++	- / -
WNV	51	f	22	WNV encephalitis	S. aureus infection, history of rheumatoid arthritis, lupus, and immunosuppressive therapy	- / +	+++ / +++	- / +++	- / -
WNV	62	m	20	WNV encephalitis	History of cardiac, lung, and brain sarcoidosis, cardiomegaly, atherosclerosis, steroid treatment	- / -	+ / +	- / +	+ / +
WNV	75	m	unkn	WNV encephalitis	History of mantle cell lymphoma, bone-marrow transplant recipient	- / -	- / ++	- / +	- / -
WNV	79	f	16	WNV encephalitis	Atherosclerosis, history of pyelonephritis, rheumatoid arthritis	- / -	- / ++	- / -	- / -

Mean: 62.6 18.3

<u>Group</u>	<u>Age</u>	<u>Sex</u>	<u>P.M.I</u>	<u>Cause of death</u>	<u>Other findings / Comorbidities</u>	<u>DG</u>	<u>CA2/3</u>	<u>CA1</u>	<u>Ent Ctx</u>
Control	47	f	21	Cardiac arrest	Emphysema, kidney atrophy, history of congestive heart failure, multiple small vessel embolisms	- / -	- / +	- / -	- / -
Control	56	f	15	Cardiogenic shock	Coronary artery disease, pericardial metastatic carcinoma, history of hepatitis C, transplant recipient	- / -	- / -	- / -	- / -
Control	57	m	4	Cardiac arrest	Atherosclerosis, history of prostate cancer, emphysema, hypertension	- / -	- / -	- / -	- / -
Control	60	m	17	Cardiac arrest	History of cardiac arrest, atherosclerosis, cardiomegaly, emphysematous changes	- / -	- / -	- / -	- / -
Control	60	f	12	Cardiac arrest	History of cerebral ischemic stroke (MCA), gram-negative sepsis	- / -	- / -	- / -	- / -
Control	65	m	17	PEA cardiac arrest	Bronchopneumonia, chronic obstructive pulmonary disease, history of myocardial infarction	- / -	- / -	- / -	- / -
Control	72	m	25	PEA Cardiac arrest	Atherosclerosis, history of congestive heart failure, history of hypotension	- / -	- / -	- / -	- / -
Control	84	f	39	Undetermined	Renal disease, myocyte hypertrophy, pulmonary fibrosis, history of sepsis	- / -	- / -	- / -	- / -

Mean: 62.6 18.8

Supplementary Table 6 – List of primers used in QPCR analyses.

	<u>Forward 5' - 3'</u>	<u>Reverse 5' - 3'</u>
C1QA	CGGGTCTCAAAGGAGAGAGA	TATTGCCTGGATTGCCCTTC
C2	CGGTGGAATTCACCCCTCAG	GGTGTGATGTGAGCTAGACCT
C3	CCAGCTCCCCATTAGCTCTG	GCACTGCCTCTTAGGAAGTC
C4B	ACTTCAGCAGCTTAGTCAGGG	GTCCTTGTTTCAGGGGACAG
C5	GAACAAACCTACGTCATTCAGC	GTCAACAGTGCCGCGTTT
CRRY	ATGGAGGTCTCTCTCGGAGT	GGCCGAAGGCTACAAGGAG
CX3CR1	ACCGGTACCTGCCATCGT	ACACCGTGCTGCACTGTCC
DAP12	GAGTGACACTTCCCAGATG	CCTTGACCTCGGGAGACC
DLG2	TGACAGAGGAACAAGCCAAGA	CGTTGTCAGAGGTGCAGTAGC
FcER1G	ATCTCAGCCTGTATCTGTTCT	ACCATAAAAAACAGGACAGCAT
FcGR2B	ATCTTGCTGCTGGACTCAT	TGACTGTGGCCTAACGTG
GAPDH	GGCAAATTCAACGGCACAGT	AGATGGTATGGGCTTCCC
GRIN1	GGGACAACACTCAAGCGTCCAGA	GCAGCCAGTTCCACGCAGTA
GRM5	ACCAACCAACTGTGGACAAAG	CAAGAGTGTGGGATCTGAATTGA
RAC2	GACAGTAAGCCGGTGAACCTG	CTGACTAGCGAGAAGCAGATG
SERPING1	TAGAGCCTCTCAGATCCGA	ACTCGTTGGCTACTTACCCA
WAS	CCAGCCGTTCAGCAGAACAT	GGTTATCCTTCACGAAGCACA